

Aquatic Animal Drug Efficacy and Safety Studies:

Who said this was a
cake-walk ?

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Jim Bowker
USFWS, AADAP Program
Bozeman, MT

Presentation Overview

- Drug approval requirements
- Draft label claims
- Research study protocol development
- What it takes to gain an all fish label claim
 - Efficacy - or “taking the show on the road”
 - Target animal safety – or “I didn’t mean to dot the T and cross the I”

Technical Sections

- Any of the unique data sets comprising the NADA
- Combined, each TS provides the necessary documentation (i.e., proof) that the new drug is:
 - Effective, as claimed on the label
 - Safe to the target animal
 - Safe for people to consume (in the case of food animals)
 - Safe to the environment
 - Safe to people involved in the manufacture, administration, etc.
 - Manufactured in a manner to provide a consistent product, and hence, consistent results.

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Where to start??

- Start with the draft label claim!
- Experimental design should be driven by how the product will be used
 - Is the label going to be broad or narrow?
 - Approved for use on many fish species?
 - Approved for use for many claims (i.e., disease, sedation)?

Label Claim

Sponsor's View vs. Reality

➤ Example #1 – AQUI-S®

1. Use to sedate all fish for transportation, handling, and surgical procedures
2. Use to sedate all freshwater salmonids for handling and management procedures

➤ Example #2 - Aquaflor™

1. Use to control mortality in all fish caused by pathogens susceptible to florfenicol
2. Use to control mortality in all freshwater reared salmonids to control mortality caused by coldwater disease

Write the Protocol “...and away we go”

- Hold up....we're not quite ready...
 - Obtain CVM concurrence (i.e., acceptance)
 - CVM's Aquaculture Team and Statistical Group review protocol...and depending upon stats review – requires 3 – 6 months for each review.
 - In our experience, requires at least two revisions for CVM acceptance
 - Stats team not comprised of “fish people”

CVM-Accepted Protocol

➤ Letter states

- “...we fundamentally agree with...and will not later change our mind unless...”
- “However, we make no commitment that the data obtained from a study implementing your protocol will support an approval.”

➤ Let's get started

Pivotal Field Efficacy Studies

Requirements

Requirements

- Demonstrate effectiveness for every disease claim
- Demonstrate effectiveness against a “U.S.” pathogen
- Demonstrate effectiveness on 2 – 3 representative coldwater, coolwater, and warmwater fish species (a fish is not a fish is not a fish)
- Adhere to appropriate Guidance Documents (#85)
- Assay drug dose

Simple Solution

- Develop “robust” models for major diseases (BGD, columnaris, coldwater disease, furunculosis, MAD, etc.)
- Conduct efficacy studies in the “lab” using fish infected using a disease model
- However...FDA has not yet decided if and how disease model/efficacy studies will be utilized....can they replace field efficacy trials? Or reduce the number of trials required? Or will they be “supportive?”

Not so simple solution

- Conduct field-based studies using sick fish (natural disease outbreak)
- Find such sites to test representative fish species for each disease to be included on the label
- Plan the “2 for 1” - to account for spontaneous recovery, concomitant diseases, confounding factors
- All fish label claim requires 12 - 18 separate studies for each disease claim

Challenges

Logistical

- Identify study site(s) with historical record of incidence of disease (track 'em down)
- Identify willing study Investigator and Monitor
- Timely start of study
- Get AADAP staff and equipment (including medicated feed) to the study site

Challenges

Biological, Culture, and Environmental

- Virulence of the pathogen
- Systemic and external pathogen?
- Pathogen sensitivity
- Concomitant pathogens
- Reinfection
- Stress of moving fish from the reference population to test tanks
- Spontaneous recovery
- Contaminated feed
- Plugged water lines
- Change in “source” water

Summary

- Challenges associated with “successful” completion of field efficacy trials
- Approved labels will be restricted by the field efficacy studies completed and accepted
- “We” can overcome these obstacles – but our batting average will never be 1,000
- Level of restriction on labeled use will be dependant upon willingness of “new” Investigators to get directly involved

Target Animal Safety Studies

Requirements

Requirements

- Lab-based studies using healthy fish
- Demonstrate an “adequate” margin of safety associated with the highest proposed dosage under “most sensitive” conditions
- Determine how much is enough
- Comply with GLP regulations and “pass” FDA in-life phase inspection
- Archive data, reports, and stats output, and wet tissues... and pass FDA data inspection

Biggest Challenges

- Timely dialogue between researchers, CVM's Aquaculture Team reviewer, and stats
- Staying on top of the GLP requirements
- How many fish species to test
 - HCG – 4 fish species
 - H₂O₂ – 14 fish species
 - AQUI-S® - 6 fish species?
- Access to various life – stages of fish for preliminary testing

Summary

- Lab-based studies on healthy fish much easier than field-based studies on sick fish
- Minimize surprises – communicate with CVM frequently; keep asking questions, you might finally ask the right one
- Develop and maintain GLP attitude
- Plan ahead (way ahead) for access to various species and sizes of fish

QUESTIONS?

Anyone?

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